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Journal of the American College of Cardiology Vol. 45, No. 12, 2005
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.12.079

Relationship Between Carotid Artery Intima-Media Thickness and Brachial Artery Flow-Mediated Dilation in Middle-Aged Healthy Men

Raymond T. Yan, MD, MASc,* Todd J. Anderson, MD, FRCPC, FACC,† Francois Charbonneau, MD, MSc, FRCPC, FACC,† Lawrence Title, MD, FRCPC, FACC,‡ Subodh Verma, MD, PhD,§ Eva Lonn, MD, MSc, FRCPC, FACC*., on behalf of the FATE Investigators

Hamilton, Calgary, Halifax, and Toronto, Canada

OBJECTIVES We aimed to determine the relationship between carotid intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) in healthy middle-age men.

BACKGROUND Carotid IMT and brachial artery FMD are frequently used as surrogate measures of subclinical atherosclerosis. Whereas carotid IMT identifies early structural abnormalities, brachial artery FMD, considered a bioassay of endothelial function, measures functional vascular integrity. The relationship between carotid IMT and brachial artery FMD has not been well studied.

METHODS We measured traditional risk factors, carotid IMT, and brachial artery FMD in 1,578 middle-aged men without known cardiovascular disease and analyzed the relationship between carotid IMT and brachial FMD.

RESULTS Carotid IMT correlated with age, systolic blood pressure, body mass index, fasting glucose, total and low-density lipoprotein (LDL) cholesterol, and with the overall Framingham risk score ($p < 0.001$ for all), whereas impaired brachial artery FMD correlated with systolic and diastolic blood pressure ($p < 0.01$). No relationship was observed between carotid IMT and brachial artery FMD for the entire cohort ($r = -0.006$, $p = 0.82$) and in subgroups defined by traditional risk factors or by quintiles of carotid IMT and brachial FMD.

CONCLUSIONS In middle-aged healthy men, there is no significant correlation between carotid IMT and brachial artery FMD. This finding suggests that these are unique, independent surrogates that measure different aspects and stages of early atherosclerosis. Further studies are needed to define their role in clinical research and in cardiovascular risk assessment. (J Am Coll Cardiol 2005;45:1980–6) © 2005 by the American College of Cardiology Foundation

It has been suggested that "atherosclerosis imaging may enhance the detection and treatment of patients at risk for coronary heart disease" (1). Proposed noninvasive atherosclerosis imaging techniques that may improve current risk stratification include carotid ultrasound (US) and brachial artery reactivity testing. High-resolution US measurements of carotid artery intima-media thickness (IMT) identify and quantitate early *structural* vascular abnormalities (2,3). Increased carotid IMT correlates with cardiovascular (CV) risk factors (4–6) and is a potent independent predictor of myocardial infarction and stroke (6–8). Brachial artery flow-mediated dilation (FMD) is an in vivo indicator of vascular endothelial *function* (2,9,10) and was also shown to correlate with various CV risk factors (9–11) and to have prognostic significance (12–14), albeit in much smaller studies that require further confirmation.

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Several previous studies in patients with cardiovascular disease (CVD) or major risk factors have reported inverse correlations between carotid IMT and brachial artery FMD (15–19). These studies were small, however (ranging from 20 to 150 study participants), and need to be interpreted with caution. Moreover, the relationship between carotid IMT and brachial artery FMD has not been adequately evaluated in apparently healthy individuals without CVD. This relationship may be particularly relevant in those subjects considered to be at low and intermediate risk of future events based on current risk stratification algorithms, as they are expected to benefit most from early atherosclerosis detection.

The Firefighters And Their Endothelium (FATE) study is an ongoing prospective longitudinal cohort study designed to assess the relationship among endothelial function, emerging and traditional CV risk factors, and, ultimately, clinical events (20). The current report describes the determinants of carotid IMT and brachial artery FMD and examines the correlation between these two measures of subclinical atherosclerosis in the FATE study participants.

From the *Department of Medicine, Division of Cardiology, McMaster University, Hamilton, Canada; †Department of Medicine, Division of Cardiology, University of Calgary, Calgary, Canada; ‡Department of Medicine, Division of Cardiology, University of Dalhousie, Halifax, Canada; and §Division of Cardiovascular Surgery, University of Toronto, Toronto, Canada. Supported by grants from the Canadian Institute of Health Research, the Heart and Stroke Foundation of Canada, and Pfizer Canada.

Manuscript received October 6, 2004; revised manuscript received November 16, 2004, accepted December 6, 2004.

Abbreviations and Acronyms

BMI = body mass index
CV = cardiovascular
CVD = cardiovascular disease
FATE = Firefighters And Their Endothelium study
FMD = flow-mediated dilation
IMT = intima-media thickness
LDL = low-density lipoprotein
US = ultrasound

METHODS

Study design and study population. The design and objectives of the FATE study have been previously published (20). In summary, this is a prospective cohort study of risk factors and predictors of CV events.

Between March 1999 and October 2003, 1,578 active and retired Canadian firefighters from Calgary and Red Deer, Alberta (n = 834); Toronto and Hamilton, Ontario (n = 403); Montreal, Quebec (n = 251); and Halifax, Nova Scotia (n = 90) were enrolled. All assessments were performed at four research centers (Calgary, Hamilton, Montreal, and Halifax). This cohort was selected as representative of middle-aged men at low to moderate CV risk. Subjects were excluded if they had known vascular disease. The study was approved by the ethics committee of each participating institution, and study participants provided written informed consent. Traditional and emerging CV risk factors were measured, and long-term follow-up is planned. Measurements of carotid IMT and brachial artery FMD were obtained in all study participants. The primary objective of the FATE study is to determine whether the measurement of endothelial function by brachial artery FMD is an independent predictor of CV events in this population. The evaluation of the relationship between carotid IMT and brachial artery FMD was a prespecified study objective.

US methods. Carotid IMT and brachial artery FMD examinations were performed at the four participating centers, each with an established, experienced research US laboratory, using SONOS 5500 (Andover, Massachusetts) or Acuson/Acoustic Response Technology ART 1 imaging systems (Mountain View, California) equipped with high-resolution 7.5 to 10 MHz linear phase-arrayed vascular transducers (within each center, all US examinations were performed using the same imaging system).

The anatomic extent of subclinical atherosclerosis was measured by quantitative B-mode US of the far wall of the right common carotid artery. All study sonographers underwent standardized training and used a common and extensively validated imaging protocol. Reproducibility and adherence to the imaging protocol were verified for each sonographer. The imaging protocol consisted of identification of the flow divider between the internal and external carotid arteries, followed by a circumferential scan of the far wall of the right common carotid artery, defined as the arterial segment starting 1 cm below the flow divider and extending 1 cm distally. The circumferential scan aimed to identify the region of this arterial segment with the highest IMT. All US examinations were recorded on S-VHS tapes and subsequently digitized and analyzed offline at the Core Carotid US Laboratory in Hamilton by one of three certified readers blinded to all clinical information, using the Image-Pro V4.5.1 software (Glen Burnie, Maryland). The Core Laboratory has extensive experience using this technique, with a high degree of reproducibility and accuracy in previous large epidemiologic studies and clinical trials (21,22). For each study participant, a minimum of three frames of the far wall of the right common carotid artery were digitized and measured. Measurements were done by tracing the leading edge of the lumen-intima and the media-adventitia interfaces, which yielded a segment mean IMT (the average thickness across the 1-cm segment − mean carotid IMT) and a segment maximum IMT (the single highest measurement between two opposing points on these interfaces − maximum carotid IMT). The frames with the highest measurements were chosen. Repeat measurements were obtained in 80 randomly chosen scans. The within- and between-reader intraclass correlation coefficients for repeat measurements ranged from 0.92 to 0.96 and are similar to previous data from our laboratory and consistent with high measurement reproducibility.

Endothelial function was evaluated by measurements of FMD of the brachial artery in response to hyperemia according to previously described and extensively validated methodology (2,9,23). Participants were free of recent fire exposure or exposure to vasoactive medications. The right brachial artery immediately above the antecubital fossa was imaged using B-mode US, and flow was measured using pulsed-wave Doppler. Simultaneous electrocardiographic recordings were obtained and displayed on the on the US system video monitor. Baseline imaging was followed by 5-min occlusion of arterial flow, achieved by inflation of a pneumatic cuff above the antecubital fossa (upper arm occlusion) to suprasystolic pressures. Following deflation of the pneumatic cuff the brachial artery was imaged continuously for 3 min (reactive hyperemia, endothelium-dependent dilation). A repeat baseline scan was obtained after a 10-min rest. Thereafter, brachial artery flow and diameter changes in response to sublingual nitroglycerin (0.3 mg) were recorded (endothelium-independent dilation). All sites used a common scanning protocol verified by the Core Brachial US Laboratory in Calgary, and all measurements were performed by a single experienced technician at the Core Laboratory. Two sequential diastolic frames (taken at the tip of the R-wave on the electrocardiogram) for the baseline, reactive hyperemia, repeat baseline, and nitroglycerin stages were digitized using an analog-to-digital converting board. Straight segments of the artery (10 mm in length) were chosen. Computer-assisted edge detection brachial analysis software (DEA, Vasometrix, Montreal) was used to calculate brachial artery diameters.

The two frames were averaged for each intervention. Endothelium-dependent FMD was defined as the maximal percent change in brachial artery diameter (between 60 and 90 s) after reactive hyperemia compared to baseline. The intraobserver and interobserver variability for repeat measurements at the Core Laboratory are 0 ± 0.07 mm and 0.05 ± 0.16 mm, respectively (24). To document scanning reproducibility, 50 subjects had repeat FMD testing 6 to 12 months after initial evaluation. The group mean was similar on both occasions, 8.2 ± 3.2% versus 8.3 ± 2.8%, and the mean of the absolute difference between determinations for each subject was a very favorable 1.8 ± 1.6%.

Statistical analysis. Continuous variables are expressed as means ± SD and discrete variables as counts and percentages. Because carotid IMT measurements were not normally distributed, logarithmic transformation was used. Means were compared using analysis of variance or the Student *t* test. Pearson's correlation was used to test bivariate correlations and results were verified using the nonparametric Spearman's rank correlation test. Multivariate linear regression analysis with backward elimination was used to determine the independent predictors of carotid IMT and of brachial FMD and to test the relationship between carotid IMT and brachial FMD (in this analysis carotid IMT was the dependent variable and brachial FMD was tested as an independent predictor) in models including classic risk factors. The relationship between carotid IMT and brachial FMD was tested for the entire cohort, in subgroups defined by traditional risk factors, and in subsets divided by quintiles of carotid IMT and by quintiles of brachial FMD (within each fifth, Pearson's and Spearman's rank bivariate correlation tests were performed). Statistical significance was defined as two-sided $p < 0.05$. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Study population. Demographic data, CV risk factors, carotid IMT, and brachial FMD measurements are shown in Table 1. By design, the cohort was predominantly male. Participants were commonly overweight. Relatively few study participants reported current smoking or a history of diabetes or hypertension. On average, blood pressure, cholesterol, and fasting plasma glucose levels were within target ranges for primary disease prevention. The average 10-year risk for coronary heart disease calculated according to the Framingham model (25) was 8.2%, consistent with a relatively low-risk population.

The average mean and maximum carotid IMT measurements were 0.72 ± 0.18 mm and 0.73 ± 0.19 mm, respectively, similar to previous published data in similar populations (26). Mean brachial artery FMD was 8.59 ± 4.05%, lower than 10%, which is the generally accepted normal lower range for this test. A significant number of subjects, 1,106 (70.1% of the study population), had attenuated FMD (<10%).

Table 1. Characteristics of the FATE Study Participants (n = 1,578)

Characteristic	Number (%)
Male gender	1,574 (99.7)
Hypertension	172 (10.9)
Diabetes	41 (2.6)
Current smoker	190 (12.0)

Characteristic	Mean ± SD	Median
Age (yrs)	49.37 ± 9.92	48.87
Systolic blood pressure (mm Hg)	128.15 ± 16.93	126.00
Diastolic blood pressure (mm Hg)	81.64 ± 10.00	80.00
BMI (kg/m^2)	28.48 ± 3.62	27.93
Total cholesterol (mg/dl)	203.40 ± 38.90	202.63
LDL cholesterol (mg/dl)	126.89 ± 32.60	126.83
HDL cholesterol (mg/dl)	48.29 ± 10.90	47.18
Triglycerides (mg/dl)	147.92 ± 105.40	120.46
Fasting glucose (mg/dl)	96.12 ± 17.38	93.60
Framingham risk score	3.99 ± 3.19	4.00
Framingham risk at 10 yrs (%)	8.17 ± 6.76	7.00
Mean carotid IMT (mm)	0.72 ± 0.18	0.70
Maximum carotid IMT (mm)	0.73 ± 0.19	0.76
Brachial artery FMD (%)	8.59 ± 4.05	8.20

BMI = body mass index; FMD = flow-mediated dilation; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein.

Correlations between traditional cardiovascular risk factors and carotid IMT. Study participants with a history of hypertension had higher carotid IMT than those without (0.81 ± 0.20 mm vs. 0.70 ± 0.18 mm, $p < 0.0001$ for mean carotid IMT; and 0.82 ± 0.21 mm vs. 0.72 ± 0.18 mm, $p < 0.0001$ for maximum carotid IMT), as did those with a history of diabetes compared to those without (0.81 ± 0.22 mm vs. 0.71 ± 0.18 mm, $p = 0.001$ for mean carotid IMT; and 0.82 ± 0.22 mm vs. 0.73 ± 0.18 mm, $p = 0.002$ for maximum carotid IMT). Trends toward higher carotid IMT were observed for current smokers versus those who denied current smoking (0.72 ± 0.16 mm vs. 0.71 ± 0.18 mm for mean carotid IMT and 0.74 ± 0.17 mm vs. 0.72 ± 0.19 mm for maximum carotid IMT), although these differences did not reach statistical significance. Bivariate correlations between carotid IMT and measured traditional CV risk factors are summarized in Table 2. Both mean and maximum carotid IMT correlated with age, systolic blood pressure, body mass index, total and LDL cholesterol, and fasting plasma glucose ($p < 0.001$ for all). Similar results were obtained using nonparametric analyses (data not shown). Importantly, both mean and maximum carotid IMT had highly statistically significant correlations of moderate magnitude with the overall Framingham risk score ($r = 0.38$, $p < 0.001$; and $r = 0.37$, $p < 0.001$, respectively). In multivariate analyses, both mean and maximum carotid IMT were independently correlated with age and with systolic and diastolic blood pressure, and maximum carotid IMT also correlated with LDL cholesterol concentration.

Table 2. Bivariate Correlations (Pearson's Correlation Coefficients) Between Cardiovascular Risk Factors and Ultrasound Measures of Subclinical Atherosclerosis and Endothelial Dysfunction

Risk Factor	Mean Carotid IMT*	Maximum Carotid IMT*	Brachial Artery Flow-Mediated Dilation
Age (yrs)	+0.480†	+0.458†	−0.010
Systolic blood pressure	+0.187†	+0.179†	−0.078‡
Diastolic blood pressure	+0.012	+0.008	−0.077‡
BMI	+0.122†	+0.113†	−0.024
Total cholesterol	+0.097†	+0.102†	−0.015
LDL cholesterol	+0.093†	+0.102†	0.000
HDL cholesterol	0.000	−0.006	+0.012
Triglycerides	+0.036	+0.035	−0.017
Fasting glucose	+0.097†	+0.102†	−0.031
Framingham risk score	+0.379†	+0.367†	−0.019

*Log transformed; †$p < 0.001$; ‡$p < 0.01$.In multivariate analyses, age and systolic and diastolic blood pressure were significant independent predictors of both average and maximum carotid IMT ($p < 0.01$), and LDL cholesterol concentration was an independent predictor of maximum IMT ($p < 0.01$). Only systolic blood pressure was independently associated with brachial artery FMD ($p = 0.001$).
Abbreviations as in Table 1.

Correlations between traditional cardiovascular risk factors and brachial artery FMD. Brachial artery FMD did not differ significantly among study participants with or without a history of hypertension, diabetes, or current smoking. As shown in Table 2, there was a modest inverse correlation between brachial artery FMD and systolic and diastolic blood pressure in univariate analyses, suggesting that study participants with higher blood pressure had more abnormal endothelial function. However, there were no significant correlations between brachial artery FMD and other measured individual risk factors and the overall Framingham risk score ($r = -0.019$, $p = NS$). In multivariate analysis, only higher systolic blood pressure was independently predictive of lower brachial artery FMD ($p = 0.001$).

Relationship between carotid IMT and brachial artery FMD. Adequate measurements of both carotid IMT and brachial artery FMD were obtained in 1,557 study participants (98.7%). There was no significant correlation between brachial artery FMD and mean carotid IMT ($r = -0.006$, $p = 0.82$) or maximum carotid IMT ($r = -0.012$, $p = 0.65$) (Fig. 1). The lack of an overall correlation was consistent in nonparametric correlation analyses (Table 3). Because of the known impact of smoking on brachial artery FMD, these relationships were examined in analyses stratified by smoking status. No significant correlations were found. Subjects with and without abnormal endothelial response, defined as brachial artery FMD <10%, did not differ significantly in their measured mean or maximum carotid IMT (mean carotid IMT: 0.72 ± 0.18 mm vs. 0.71 ± 0.17 mm, $p = 0.59$; maximum carotid IMT: 0.73 ± 0.18 mm vs. 0.72 ± 0.18 mm, $p = 0.58$). No significant differences in brachial artery FMD were noted in those subjects with mean and/or maximum carotid IMT below and above the mean or the median value for the entire cohort. In multivariate regression models with mean and maximum carotid IMT, respectively, as dependent variables and brachial artery FMD and other variables identified in bivariate analysis to be significantly correlated with carotid IMT as predictors, brachial artery FMD was not an independent predictor of either mean (beta coefficient = −0.052; $p = 0.70$) or maximum carotid IMT (beta coefficient = −0.015; $p = 0.912$).

The impact of traditional CV risk factors on the relationship between carotid IMT and brachial artery FMD was evaluated in prespecified subgroup analyses. There was no significant correlation between carotid IMT (both mean and maximum IMT) and brachial artery FMD among current smokers or subjects with hypertension (history of hypertension or blood pressure >140/90 mm Hg) or diabetes (history of diabetes or fasting blood glucose >7.0 mmol/l).

We divided the study participants by quintiles of carotid IMT, i.e., in subsets defined by various degrees of structural vascular abnormalities (Table 3), and evaluated the correlation between carotid IMT and brachial artery FMD within each fifth. There were no significant correlations. We then divided the study population by quintiles of brachial artery FMD, i.e., in subsets defined by various degrees of functional vascular abnormalities (Table 3), and evaluated correlations between carotid IMT and brachial artery FMD within each fifth. No significant correlations were observed.

All correlation analyses between carotid IMT and brachial artery FMD were also evaluated in analyses stratified by study center. Results were similar, with lack of correlation between carotid IMT and brachial artery FMD for the entire cohort and within each of the four research centers.

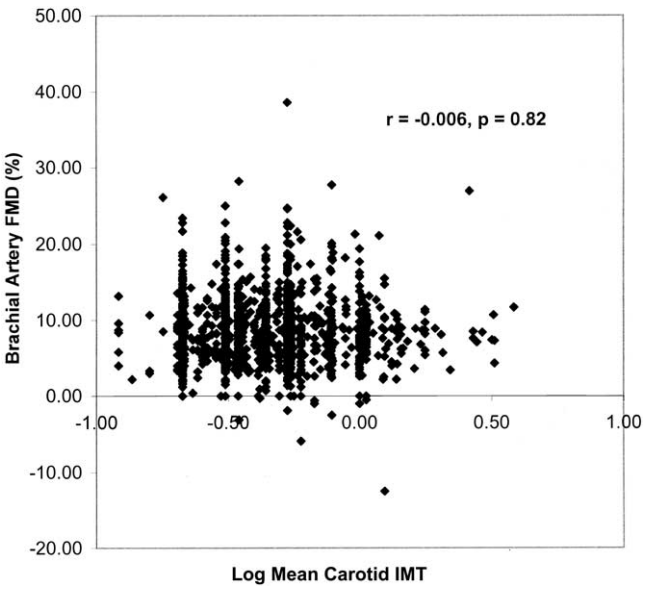

Figure 1. Correlation between mean carotid intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD).

Table 3. Relationship Between Carotid IMT and Brachial Artery FMD Across Quintiles of Carotid IMT and Brachial FMD

	Quintile of Mean Carotid IMT (mm)					
	1	**2**	**3**	**4**	**5**	
	0.51 ± 0.08	**0.61 ± 0.09**	**0.69 ± 0.03**	**0.76 ± 0.01**	**0.98 ± 0.17**	**Spearman's Rho**
Brachial artery FMD (%)	8.4 ± 3.7	8.7 ± 3.8	8.6 ± 4.0	8.9 ± 4.2	8.3 ± 4.3	−0.004; p = 0.885
	Quintile of Brachial Artery FMD (%)					
	1	**2**	**3**	**4**	**5**	
	3.8 ± 1.8	**6.4 ± 0.6**	**8.2 ± 0.5**	**10.0 ± 0.6**	**14.6 ± 3.5**	
Mean carotid IMT (mm)	0.71 ± 0.17	0.73 ± 0.19	0.73 ± 0.20	0.71 ± 0.16	0.71 ± 0.17	

The Spearman's rank correlation coefficient for mean carotid IMT and brachial artery FMD for the entire cohort was −0.004; p = 0.885; similarly, there was no significant correlation between mean carotid IMT and brachial FMD in study participants within any fifth of mean IMT and any fifth of brachial artery FMD.
Abbreviations as in Table 1.

DISCUSSION

The main finding of our study is the lack of correlation between measurements of carotid IMT and brachial artery FMD in a cohort of middle-aged men without CVD and with relatively few risk factors. This finding could have several explanations: 1) it is possible that, contrary to current prevalent beliefs, carotid IMT and/or brachial artery FMD are not valid measures of early vascular disease; 2) it is possible that the research techniques employed, specifically the US measurements, were not adequate and allowed for noise, which may have obscured an existent correlation; and finally, 3) carotid IMT and brachial artery FMD may provide *distinct* information identifying different stages in atherogenesis. We believe the latter to principally account for our findings, although we cannot exclude the possibility that brachial artery FMD may be less informative in this cohort than previously thought.

Thus, both carotid IMT and brachial artery FMD are well-validated techniques (2,3,9,23). Both are highly reproducible when performed by experienced technicians in a research environment (2–13,21–24). Carotid IMT was shown to correctly identify histologic abnormalities and to correlate with traditional and emerging cardiovascular risk factors (2–6). It correlates with prevalent CV disease (4,21) and, importantly, it was a potent independent predictor of incident myocardial infarction and of stroke in large cohort studies (6–8). Moreover, interventions known to decrease the atherosclerotic process and to prevent clinical events, such as statins, angiotensin-converting enzyme inhibitors, and other blood-pressure-lowering agents (2,3,22), were shown to retard the progression of carotid IMT. Several lines of evidence suggest that brachial artery FMD is a valid measure of vascular integrity. The vasomotor response of the brachial artery in response to hyperemia measured by high-resolution US was shown to be nitric-oxide-dependent and to correlate well with coronary endothelial-dependent vasomotor function (9,23,24). Interventions that improve vascular health and increase the bioavailability of nitric oxide, such as statins and angiotensin-converting enzyme inhibitors, were shown to improve brachial artery FMD (9,27,28). Finally, although examined to date only in relatively small studies that are often retrospective and requiring further confirmation, emerging evidence suggests that brachial artery FMD may be an independent predictor of outcomes (12–14). It is essential, however, to realize that the data correlating brachial artery FMD to coronary endothelial function and to CV outcomes are derived primarily from studies in individuals with manifest CV disease or at high risk for CV disease, with very limited information on low- and moderate-risk groups.

The notion that technical limitations in performing the US assessments may have obscured an existent correlation is not justified. Indeed, all US scans were performed at experienced research US laboratories, following common standardized protocols and using rigorous quality control measures; all measurements were obtained at the Core US Laboratories, which have extensive experience with these techniques. Scanning and measurement reproducibility were high. Moreover, analysis of the correlation between carotid IMT and brachial artery FMD within each center and for the entire cohort stratified by study center yielded similar results.

Therefore, we believe that our findings support the conclusion that in apparently healthy individuals with relatively few risk factors, carotid IMT and brachial artery FMD do indeed provide distinct, independent information about the complex atherosclerotic process. Such information may be temporarily dissociated, with abnormalities in endothelial function preceding anatomic lesion formation. However, we do recognize the possibility that brachial artery FMD, which is less well validated in prospective studies than carotid IMT and did not correlate with classic risk factors in our study, may be of limited value in a relatively healthy population, which, in the absence of major sustained alterations to vascular function imposed by the prolonged exposure to traditional risk factors, may be more susceptible to the impact of short-term (possibly transient) factors. Several previous small studies (some lacking methodologic details) have evaluated this relationship and do generally report significant correlations (15–19). We believe that a strong publication bias may have resulted in underreporting of negative studies. Moreover, with few exceptions (16), previous studies have focused on high-risk patients.

We also report associations between traditional CV risk factors and carotid IMT and brachial artery FMD, respectively. In univariate analysis, carotid IMT correlated with age, systolic blood pressure, body weight and body mass index, total and LDL cholesterol, fasting blood glucose, and a history of hypertension and of diabetes. Importantly, there was a significant correlation of moderate magnitude with the overall Framingham risk score. In multivariate analysis, age, blood pressure, and LDL cholesterol concentration were independent predictors of carotid IMT. Our observations are consistent with previous reports (2–7). Some risk factors appear only modestly correlated with carotid IMT, which may be related to overall good risk factor control in our population and the data for carotid IMT and for many risk factors clustering around average ("normal") population values.

By contradistinction, brachial artery FMD was correlated only with blood pressure. The poor correlation between brachial artery FMD and traditional risk factors is puzzling and may reflect the complexity of endothelial function, which is the result of the interplay of a wide range of systemic factors, including those acting for years or decades (CV risk factors), but also acute influences. Previous studies relating brachial FMD and risk factors have yielded mixed results and have suffered from small sample sizes, different methodologies, and heterogeneous populations. In one of the larger previous studies, Celermajer et al. (11) assessed brachial artery FMD in 500 healthy subjects. In multivariate analysis, the strongest determinants were age and cigarette smoking. However, no relationship between lipid parameters or blood pressure and brachial artery FMD was found. In a population of young adults (n = 326), Leeson et al. (29) demonstrated a weak relationship between n-3 fatty acids and FMD in certain subgroups, but no relationship with standard risk factors. In our study, a weak relationship between FMD and blood pressure is identified. However, there was no correlation with age, other risk factors, or Framingham risk scores. These findings suggest that brachial artery FMD could represent a unique measure of vascular health, which may be influenced significantly by parameters currently not measured. Such parameters may overwhelm the influences of traditional risk factors, especially in a generally healthy population with a low prevalence of traditional risk factors.

Our findings pertain solely to the population studied, middle-aged, apparently healthy men without CVD, and should not be generalized. Further studies in various populations are needed.

In conclusion, in a relatively healthy cohort of middle-aged men, no significant correlation exists between carotid IMT and brachial artery FMD. This finding may be related to a temporal dissociation between functional and structural vascular abnormalities in a low-risk population. However, we cannot exclude the possibility that brachial artery FMD, which did not correlate with most traditional CV risk factors in our study, may not be a good measure of the sustained effect of risk factors on endothelial function in a low-risk population and may register primarily the short-term impact of various factors. Although these noninvasive measures of early structural subclinical atherosclerosis and of endothelial dysfunction may provide unique and possibly complementary information about vascular health, our findings suggest that endothelial function testing is not yet ready for "prime time" clinical use and underscore the need for well-designed large prospective studies aimed at evaluating the value of brachial artery FMD in predicting CV events. Such studies are underway (20) and may represent the ultimate test of validity for this bioassay of endothelial function.

Reprint requests and correspondence: Dr. Eva Lonn, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: lonnem@mcmaster.ca

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